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Review Article

Primary glomerulonephritis: A review of important recent discoveries

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ABSTRACT

The publication of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on the treatment of glomerular diseases in 2012 marked a milestone in this field, as it is the first time that comprehensive guidelines are provided for such disease entities. The current review focuses on major findings, both pathogenesis related and clinical, in the primary glomerulonephritis that have been made after the guidelines came into effect.

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Introduction

Certainly the most important event in 2012 was the publication of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the treatment of glomerular diseases [1]. For the first time evidence-based guidelines are now available in this field. The guidelines have taken a relatively long time to be published and are based on the knowledge available in early 2011 to mid-2011. Thus, in this review I will focus exclusively on important developments in the field of primary glomerulonephritis (GN) in 2012 and early 2013.

Immunoglobulin A nephropathy

Pathogenesis

The year 2012 has seen some advances in understanding the complex pathogenesis of immunoglobulin A nephropathy (IgAN) [2–4]. There is increasing evidence that autoantibodies play a role against poorly galactosylated IgA in the disease. These autoantibodies are largely confined to IgAN and correlate with the clinical prognosis [5,6]. Poor galactosylation of the circulating (and deposited) IgA may, among others, involve altered expression of miR-148b [7]. In addition, a recent study suggests that the fractalkine CX3CR1 contributes to the characteristic hematuria seen in IgAN [8], but the exact mechanism by which it may cause hematuria still remains elusive [9].

In an elegant mouse model, the role of the two IgA receptors, soluble CD89 (sCD89) and transferrin-receptor-1, was studied [10]. Mice with transgenic overexpression of human IgA1 and CD89 develop inflammatory renal changes, hematuria, and proteinuria. In these mice, sCD89 binds mesangial transferrin-receptor-1 and this complex induces transglutaminase-2 in the cells. The latter serves as an amplification loop, favoring the generation of more IgA1-sCD89 complexes and thus further activation of mesangial cells. Transglutaminase-2 thus may be a novel therapeutic target in IgAN, provided that this mechanism can be confirmed in the human disease.

Another rapidly evolving area is the knowledge on the genetic basis of IgAN in large populations. Genome-wide association studies have identified associations of single human leukocyte antigen (HLA) polymorphisms [11] and some proinflammatory genes [12] with the development or course of IgAN. More importantly, using such a genetic approach, we can develop a worldmap of IgAN risk [13] (Fig. 1).

Prognosis

As previously done, in 2011, a number of studies attempted to validate the histological Oxford classification of IgAN [14]. Similar to previous studies, the more recent ones again show that mainly interstitial changes (i.e., the "T" criterion of the

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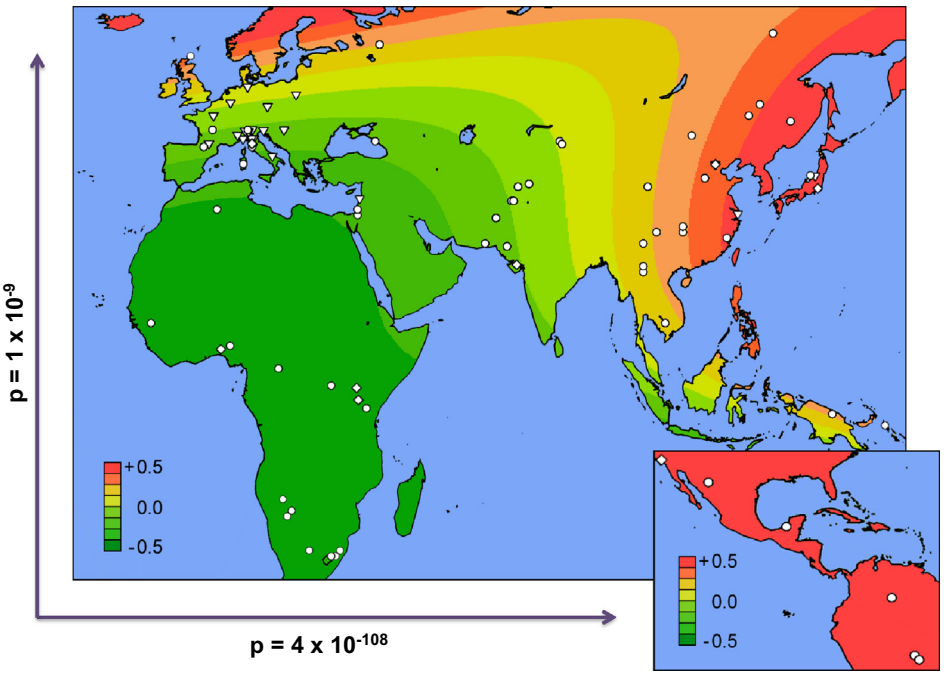

Figure 1. World-wide genetic risk for immunoglobulin A nephropathy (IgAN). Gene-wide association studies indicate different worldwide risks for IgAN. (Reprinted with permission from Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, Eitner F, Snyder HJ, Choi M, Hou P, Scolari F, Izzi C, Gigante M, Gesualdo L, Savoldi S, Amoroso A, Cusi D, Zamboli P, Julian BA, Novak J, Wyatt RJ, Mucha K, Perola M, Kristiansson K, Viktorin A, Magnusson PK, Thorleifsson G, Thorsteinsdottir U, Stefansson K, Boland A, Metzger M, Thibaudin L, Wanner C, Jager KJ, Goto S, Maixnerova D, Karnib HH, Nagy J, Panzer U, Xie J, Chen N, Tesar V, Narita I, Berthoux F, Floege J, Stengel B, Zhang H, Lifton RP, Gharavi AG. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. *PLoS Genet* 8:e1002765, 2012)

Oxford classification) allow a prognostic assessment, whereas all other parameters, in particular the more inflammatory changes ("M" and "E") performed less reliably ([15–20], Table 1). Similarly, the presence of glomerular crescents, which is not a part of the four Oxford criteria, is of inconsistent prognostic power.

Apart from histological predictors of IgAN, a Korean study demonstrated that low circulating C3 levels can also herald an adverse prognosis in IgAN patients [21]. Similarly, extraglomerular C3 deposits in Bowman's capsule and/or arterioles signal an adverse prognosis [22].

Of clinical importance is a Chinese study that describes histological features of 90 IgAN patients, who had received a kidney biopsy for isolated microhematuria [23]. Not surprisingly, these patients exhibited mostly mesangial hypercellularity ("M" in the Oxford classification) and endocapillary proliferation ("E" in the Oxford classification), i.e., mostly early and inflammatory changes. However, and very remarkably, within these relatively young patients (mostly 20–30 years old) 50% had some focal or global glomerulosclerosis, 20% had tubulointerstitial damage, and 25% had isolated glomerular crescents. Thus, the important insight gained here is that IgAN patients with a clinically excellent prognosis can exhibit even crescents and vice versa; not every crescent in IgAN necessitates immunosuppression.

Clinical aspects

A Spanish study reported on the long-term course of 141 IgAN patients, who, similar to the Chinese patients discussed earlier, had received kidney biopsies despite only minor urinary abnormalities [i.e., microhematuria or mild proteinuria with a normal glomerular filtration rate (GFR)] [24]. No patient received immunosuppression. An increase in serum creatinine of 50% or more was observed in 3.3% of cases at 10 years follow-up and in 8.9% of cases at 20 years follow-up. Of the patients, 38% developed a full clinical remission after a median duration of 48 months. However, six patients developed a proteinuria of more than 1 g/d and 42% of patients subsequently received blockers of the renin–angiotensin system (RAS).

This Spanish study therefore confirms that mild IgAN has an excellent overall prognosis. However, a few patients will progress, and currently it is not possible to identify them prospectively. It is therefore imperative that such early diagnosed IgAN patients receive annual or biannual checkups.

Based on the literature, a nephrotic syndrome is a rare manifestation of IgAN (unless there is an overlap with minimal change nephropathy). It is therefore notable that in Korea about 10% of a large patient series exhibited a nephrotic syndrome [25]. Such patients had a poor prognosis, and almost a quarter of them experienced a doubling of their serum creatinine within the subsequent 4 years. Surprisingly, however, others exhibited spontaneous remissions, a good prognosis (in particular women and patients with low initial serum creatinine levels, and a decrease of the proteinuria of $>50\%$ in 3 months). Again, these observations stress the importance of regular controls after the diagnosis.

Yet another Korean study contradicts the widespread opinion that Henoch-Schönlein purpura in adults runs a more severe course than primary IgAN [26]: when patients were matched for baseline characteristics, the course of the two diseases was not different. This study supports the general assumption that the two diseases are very similar and likely manifestations of the same disease process.

Table 1. Recent studies on the validation of the Oxford classification of immunoglobulin A nephropathy

Ref.	Country	*n*	Independent prognosis predictors	Comments
[15]	China	1,026	M, T	Crescents without prognostic relevance
[16]	China	218 (children)	T	Crescents without prognostic relevance
[17]	Korea	69	E, T	
[18]	Sweden	99 (children)	M, E, T	Crescents with prognostic relevance, but only univariate analysis
[19]	Korea	197	T	
[20]	Japan	161 (children)	M, T	Crescents with prognostic relevance

E, endocapillary proliferation; M, mesangial hypercellularity; S, glomerulosclerosis; T, tubular atrophy and interstitial fibrosis.

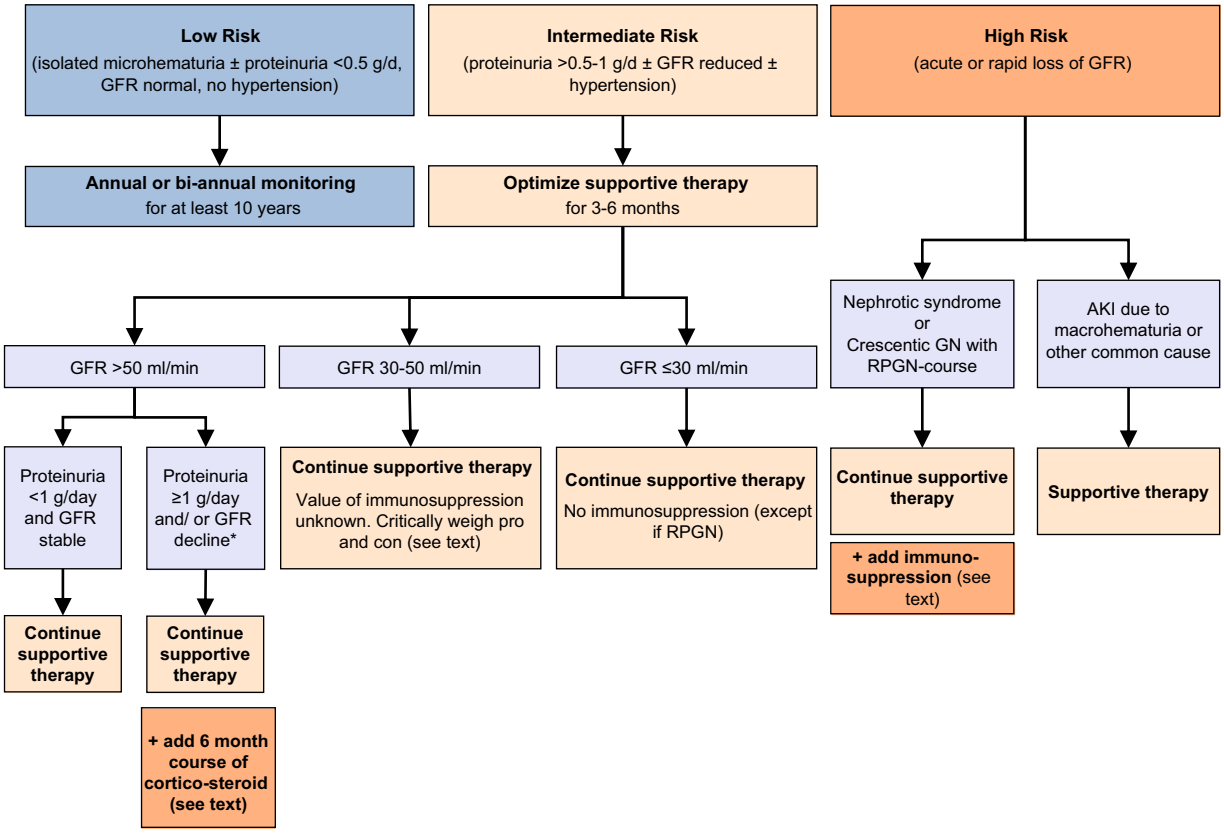

Figure 2. Therapy algorithm for immunoglobulin A nephropathy. Details of the suggested supportive therapy can be found in [28]. AKI, acute kidney injury; RPGN, rapidly progressive glomerulonephritis. Modified from [28].

Therapy

We have summarized the therapy of IgAN recently (Fig. 2) [27,28].

A new study from Hong Kong assessed the effects of low-dose angiotensin-converting enzyme (ACE) inhibitors in early IgAN [29]. Sixty patients with a proteinuria of < 0.5 g/d, normotension, and a normal GFR received 2.5 mg/d ramipril or no specific therapy. After 5 years, there were no differences between the groups and GFR loss was almost identical (-0.4 ± 2.6 mL/min/1.73 m^2 per year vs. -0.6 ± 1.6 mL/min/1.73 m^2 per year). It is very likely that the study was underpowered in view of the very slow progress of early IgAN and thus the study cannot finally answer whether such early IgAN patients benefit from RAS blockade in the very longterm.

Japanese authors continue to report on the success of tonsillectomy in IgAN [30–33]; however, a large randomized trial is still to be performed, and KDIGO, at present, does not recommend routine tonsillectomies in IgAN [1].

Corticosteroids and other immunosuppressive drugs

A meta-analysis investigated the value of corticosteroid therapy in IgAN. The study concluded that corticosteroids can retard the progress of renal failure and can reduce proteinuria [34]. Low doses (< 30 mg/d prednisone initially) are ineffective. The meta-analysis, however, also concludes that the methodological quality of available studies is low. Consequently, steroids should only be used in IgAN when supportive measures have failed (Fig. 2).

An uncontrolled Korean case series reported on 22 IgAN patients with a median eGFR of 34 mL/min/1.73 m^2 [2,35]. In the KDIGO guidelines such patients represent a dilemma, because other than optimizing the supportive therapy no

recommendations are given, as literally all randomized trials so far have excluded such patients. All Korean patients received a RAS blocker followed by 500 mg methylprednisolone i.v. every 2nd week for 6 months. Although this did not improve proteinuria, it did slow down the loss of GFR. Reportedly there were no relevant side effects.

Other uncontrolled reports describe the use of tacrolimus in "refractory IgAN" [36], where 20% of the patients experienced a decline of GFR but in 80% of patients proteinuria was lowered, as well as combined prednisolone and mycophenolate mofetil (MMF) therapy, which reduced proteinuria but did not affect serum creatinine [37]. Unfortunately, these uncontrolled studies do not help in deciding which therapy is effective in patients with IgAN. At present, KDIGO guidelines recommend neither tacrolimus nor MMF in IgAN.

Two ongoing randomized controlled trials assess the value of corticosteroids added to optimized supportive care: Our supportive versus immunosuppressive therapy of progressive IgA nephropathy (STOP-IgAN) trial [38], which will end in late 2014, and the large therapeutic evaluation of steroids in IgA nephropathy global study (TESTING study), which just started in China and Australia (NCT01560052). Another trial that has started is the pan-European NEFIgAN study, where patients will receive budenoside or placebo based on a Swedish pilot study [39].

Membranous glomerulonephritis

Pathogenesis

Autoantibodies against phospholipase-A_2-receptor (PLA2R-Ab), mostly of the IgG4 class (rarely monoclonal IgG3 [40]), can be found in about 70% of all patients with primary membranous GN. They bind to PLA2R on podocytes with the *in situ* formation of immune complexes and complement activation [41,42]. In addition to these autoantibodies, further autoantigens are being searched for in membranous GN. An Italian group repeatedly described IgG4 autoantibodies against aldose-reductase, superoxid-dismutase-2, and alpha-enolase in patients with membranous GN [43]. These antibodies occurred at lower frequency compared to PLA2R-Ab. Their pathogenetic importance remains unclear at present, because the corresponding antigens are not found in podocytes in membranous GN (in contrast to PLA2R, which is expressed *de novo*). Another potential autoantigen is synaptonemal complex protein 65 (SC65) [44].

Clinical aspects

Dutch data show a close correlation between PLA2R-Ab levels with the clinical course (i.e., disappearance of the autoantibodies during clinical remission) and proteinuria [42]. The potential clinical use of detecting PLA2R-Ab rests in the serologic diagnosis of a primary membranous GN, therapeutic stratification, and therapy monitoring. The antibodies may also aid in the differentiation between primary and secondary GN: in secondary membranous GN both circulating antibodies and PLA2R expression on podocytes are generally absent, although there are rare exceptions to this rule [45]. Detection of PLA2R autoantibodies in the circulation and PLA2R expression on podocytes is mostly concordant, and possibly the demonstration of PLA2R on podocytes is more sensitive [46]. It is presently unknown whether therapeutic decisions can be based on the course of PLA2R-Ab.

From a clinical point of view, a Spanish study is important, which demonstrates that even in patients with impaired renal function, spontaneous remissions are possible if only RAS-blockers are given [47].

Therapy

Sixteen years after its initiation, a British randomized trial in membranous GN was finally published in 2012 [48]. In this study, high-risk patients with membranous GN (i.e., those with a relatively rapid decline in GFR) were randomized to supportive therapy only ($n=38$), prednisone and chlorambucil ($n=33$), or cyclosporine ($n=37$). Only prednisone/chlorambucil lowered the risk of progression, although even this group continued to lose some GFR. Cyclosporine was not effective in this selected group of patients and was not different from supportive therapy only. Not unexpectedly, the combination therapy caused more adverse effects. Unfortunately, prednisone/chlorambucil is

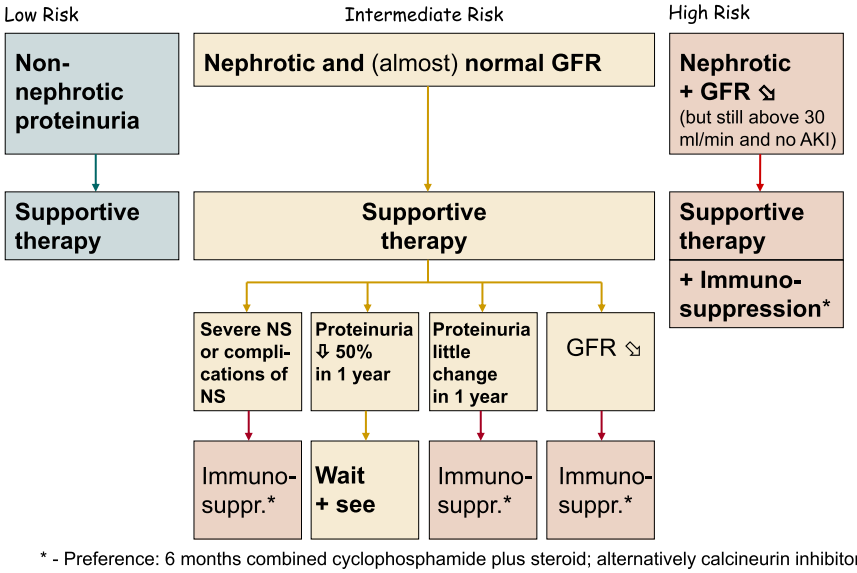

Figure 3. Therapy algorithm for membranous nephropathy. For details of the suggested immunosuppressive approach, please refer to the KDIGO 2012 guidelines [1]. AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; NS, nephrotic syndrome.

now rarely used and has largely been replaced by prednisone/cyclophosphamide. We can only assume that this combination is equally effective in these high-risk patients.

In 2012, the Italian group from Bergamo published its experience with 100 consecutive membranous GN patients treated with rituximab [49]. After a median 29-month follow-up, 65% exhibited partial or full remission, 4% were on dialysis, and 4% had died (of unrelated causes, according to the authors). Having had a prior immunosuppressive therapy was a key predictor for failure to respond to rituximab. Unfortunately, there is no information on whether the presence or absence of PLA2R-Ab also influenced rituximab responses.

At present, KDIGO still recommends a cyclophosphamide- or alternatively a calcineurin inhibitor-based first-line therapy, whereas MMF or a corticosteroid monotherapy are not suggested [1] (Fig. 3). Rituximab is still considered a second-line therapy. This view has also been shared by a very recent editorial, which, apart from the considerable cost associated with rituximab therapy, points out the risks of the rare progressive multifocal leukoencephalopathy and also notes that at least in a vasculitis study rituximab-treated patients exhibited an increased tumor risk [50]. Finally, rituximab can induce a hypogammaglobulin syndrome independently of the dose, which manifests similar to a chronic immune deficiency syndrome and may not be reversible. A prior immunosuppressive therapy may increase the risk for this latter complication. Nevertheless, others also caution against too much rituximab euphoria and demand controlled clinical trials [51,52]. Indeed, a controlled trial comparing cyclosporine versus rituximab in membranous GN is underway (NCT01180036).

Minimal change nephropathy and focal segmental glomerulosclerosis

Pathogenesis

A central discovery of the past years was the demonstration of elevated soluble urokinase receptor (suPAR) levels in the serum of focal segmental glomerulosclerosis (FSGS) patients [53]. The pathophysiological basis of how suPAR relates to nephrotic syndrome is well documented, and indeed suPAR transgenic animals developed FSGS.

Etiology and prognosis

The group that discovered suPAR in FSGS has now validated their findings in two large cohorts of 164 children and adults with primary FSGS [54]. Of the patients studied, 84% of the children and 55% of the adults exhibited elevated suPAR levels in their circulation. However, suPAR levels in the circulation also increase nonspecifically in chronic kidney disease (CKD) due to renal retention. Another puzzling finding of that study is that FSGS patients with mutations of *NPHS2* exhibited even higher suPAR levels than nongenetic FSGS cases. Finally, the first studies where the difference between suPAR levels in primary FSGS versus secondary FSGS or other glomerular diseases was not confirmed are emerging [55]. Thus, still much has to be learned about suPAR prior to recommending this as a routine clinical assessment or even as a therapeutic target in FSGS cases.

As to genetic causes of FSGS, the role of mutations in inverted formin 2 (*INF2*) as a cause of familial autosomal-dominant FSGS was better established in 2012 [56–58]. Nevertheless, the KDIGO guidelines still do not recommend routine screening for mutations in podocyte proteins in adults with FSGS as long as no family history is present. Indeed, in 26 consecutive German dialysis patients with underlying FSGS, mutations were detected only in 8% of patients and were found in *TRPC6*, *ACTN4*, *NPHS2*, and *NPHS1* with no mutations in *INF2*, *CD2AP*, and *WT1*) [59]. This was confirmed in another large cohort of sporadic FSGS patients, where *INF2* mutations were found in less than 1% of patients [56].

A clinically important issue is the distinction between minimal change nephropathy and FSGS, in particular if the latter is in an early stage. Possibly, an activation marker in glomerular parietal epithelial cells, which was discovered by us, can help in this respect [60]; at least in renal transplant biopsies the immunohistological detection of CD44 on parietal epithelium allowed a reliable distinction.

Therapy

Few studies have been reported in 2012 on the treatment of minimal change nephropathy or FSGS: (1) in an Indian study, 131 children with steroid resistance received either 12 months of tacrolimus or 6 months of i.v. cyclophosphamide boli plus steroids [61]. Compared to cyclophosphamide, tacrolimus induced more complete remissions (52% vs. 15%, respectively) and led to fewer adverse effects; (2) in a German trial, 23 children with FSGS were analyzed after induction of remission by steroid boli plus cyclosporine [62]. The subsequent maintenance therapy included alternating steroid, cyclosporine, and RAS blockers. MMF was subsequently used in 18 of the children. All were maintained in remission for >7 years, and in 30% of patients all immunosuppressants could be stopped. There were five relapses in the 23 patients, all of which responded well to repeated therapy. The authors conclude that MMF is a potent maintenance therapy in FSGS; and finally (3) a French study described the course of 17 adults with steroid-dependent minimal change nephropathy following the administration of rituximab [63]. All had previously failed other immunosuppressive approaches. Eleven of the 17 patients subsequently had no more relapses after rituximab, and nine could halt all immunosuppressants. Others were at least able to reduce their dose of immunosuppressants. There were no serious adverse effects. The reason why rituximab worked in a disease not considered to be mediated by B cells currently remains elusive.

Other primary GN

Membranoproliferative glomerulonephritis

A single case of cryoglobulinemia-triggered membranoproliferative glomerulonephritis was described, and the patient responded well to imatinib [64].

Dense deposit disease (formerly called "membranoproliferative glomerulonephritis type II") and C3 nephropathy

Following the discovery that dense deposit disease (DDD) results from unregulated complement activation via an alternative

pathway (mostly from C3 nephritis factor, i.e., C3-activating autoantibodies) [65], new therapeutic approaches have been developed for DDD. Already, single patients have received a C5 antibody, eculizumab, every other week for 1 year or longer. In some of these patients, but not all, clinical and/or histological manifestations of the disease have improved [66,67]. A first case report also describes the successful use of eculizumab in recurrent DDD after renal transplantation [68]. However, a concern for prolonged eculizumab therapy in DDD and C3 GN was raised when such patients received a second kidney biopsy after 1 year of treatment; whereas glomeruli in these diseases typically contained only C3 deposits but no Igs at baseline, after 1 year of treatment there was prominent deposition of IgG2 and IgG4 as well as IgG-kappa light chain, all components of the eculizumab molecule [69]. This deposition was histologically very similar to the disease entity known as monoclonal IgG deposition disease. Long-term consequences of these pathological changes are currently unknown.

Following the first description of C3 nephropathy in patients with an autosomal-dominant mutation in the *CFHR5* gene, further characteristics have been reported [70]. So far, the disease has only been described in patients originating from Cyprus; possibly all cases can be traced to a small mountain area. Histologically, the central finding is prominent glomerular C3 deposition with no immune complexes, obviously due to the unregulated complement activation. About 50% of the affected individuals, in particular men, develop renal failure.

Postinfectious GN

Postinfectious GNs mostly heal with no long-term sequelae. A small percentage of affected patients, however, develop a course of progressive CKD. In a report from the Mayo Clinic, it has now been proved that such patients exhibit defects in the regulation of the alternative complement pathway (e.g., mutations in complement-regulatory proteins, C3 nephritis factor, and others) [71].

Conflicts of interest

All authors declare no conflict of interest.

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